SYNTHESIS OF 2-ALKYL-5-OXOHEXANOIC ACIDS AND ESTERS AND THEIR EFFECT ON CIGARETTE SMOKE

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SUMMARY

2-Isopropyl-5-oxohexanoic acid is a degradation product of cembranoids and an important component of the acidic fraction in Oriental tobacco. It produces the hay-like odor and gives slightly grassy smell to smoke. This study is aimed at sythesising a series of 2-alkyl-5-oxohexanoic acids and their esters and determining the effect of these compounds on cigarette smoke.

4-Diethylaminobutan-2-one is obtained by a modified Mannich reaction in yields of 70%. Methiodised 4-diethylaminobutan-2-one and diethyl malonates are submitted to a thermal-induced Michael addition reaction to synthesise the acids in one step.

It is found that 2-isopropyl-5-oxohexanoic acid and its esters have a noticeable effect in sensory tests. They enhance and improve the flavor of smoke and reduce the irritation of blended type cigarettes and contribute to flue-cured type cigarettes.

Meanwhile it is revealed that the isopropyl radical in C-2 of the acids play an important role in enhancing the flavor of cigarette smoke.

INTRODUCTION

2-Isopropyl-5-oxohexanoic acid is a terpenoid acid in the acidic fraction of Oriental [1-4], flue-cured [5-7] and burley [8] tobacco. The acid is a degradation product of cembranoids and has the characteristic aroma of Oriental tobacco [2,3].

Several methods in the synthesis of 2-isopropyl-5-oxohexanoic acid have been reported [9-25], With reference to Bardhan's method [24], diethyl

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isopropylmalonate and 4-diethylaminobutan-2-one methiodide were used as starting material. Considering the difficulty to separate the condensation product, ethyl 2-ethoxycarbonyl-2-isopropyl-5-oxohexanoate, by distillation, saponification and decarboxylation were completed without separation of the condensation product in this study. 2-Methyl-and 2-ethyl-5-oxohexanoic acid were synthesised with the same method. Methyl and ethyl esters of these three acids were prepared by direct esterification.

The effect of these compounds on cigarette smoke were evaluated.

EXPERIMENTAL

DIETHYL METHYLMALONATE To a stirred mixture of dimethyl sulphate (73.2g), diethyl malonate (80g), tetrabutylammonium iodide (8.1g) and benzene (300ml), cooled to 10℃, a solution of 44% sodium hydroxide in water was added and the temperature was kept at 15~20℃. Having stirred at the same temperature for 45 min, 100ml of water were added to the mixture. The organic layer was separated and washed with water to pH7. After removal of benzene by distillation, diethyl methylmalonate (79g, 91.9% yield) was collected at 70~73℃/5mmHg, n_D^{32} 1.4067 (n_D^{20} 1.4226 in reference [26]).

Diethyl ethylmalonate and diethyl isopropylmalonate were prepared according to the method described in the reference [27].

4-DIETHYLAMINOBUTAN-2-ONE A mixture of acetone (500ml), formaldehyde (120g, 36% solution in water) and diethylamine hydrochloride (154g) was refluxed for 12 hrs. About 350ml of acetone were distilled off and a solution of 56g of sodium hydroxide in 210ml of water was added to the residue. The upper organic layer was separated and the water layer was repeatedly extracted with ethyl ether. The combined organic layer were dried over anhydrous potassium carbonate. After evaporation of ethyl ether and acetone, vacuum distillation of the residue gave 4-diethylaminobutan-2-one (155.7g) which was collected at 70~73℃/15mmHg, n_D^{21} 1.4348 (bp 84℃/30mmHg and n_D^{24} 1.4333 in reference [26]).

4-DIETHYLAMINOBUTAN-2-ONE METHIODIDE IN ETHANOL To a stirred solution of 4-diethylaminobutan-2-one (28.6g) in 30ml ethyl ether, methyl iodide (40g) in 10ml of ethyl ether was added below 5℃. The turbid mixture obtained was

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stirred below 5℃ for 30 min. and then at room temperature for 1 hr. After removing ethyl ether and unreacted methyl iodide by filtration, a white solid was obtained and then dissolved in 100ml of absolute ethanol for next step use.

2-ALKYL-5-OXOHEXANOIC ACID Diethyl alkylmalonate (0.2mol) was added to a solution of 4.6g of sodium in 150ml of absolute ethanol, the mixture was refluxed with stirring for 5 min. To the mixture, cooled in ice-salt, the above prepared solution of 4-diethylaminobutan-2-one methiodide in absolute ethanol was gradually introduced. After stirring at 0-5℃ for 5 hrs., the mixture was kept at room temperature overnight and followed by reflux for 4 hrs. About 120ml of ethanol were distilled off, the residue was refluxed with 30g of potassium hydroxide in 24ml of water for 1 hr., then the mixture was diluted with 60ml of water. Distilling off the ethanol as completely as possible, the alkaline residue was acidified to pH3 with dilute hydrochloric acid and extracted repeatedly with ethyl ether. After removal of the ethyl ether by distillation the reidue was heated at 130-140℃ until evolution of carbon dioxide ceased. Vacuum distillation of the residue gave 2-alkyl-5-oxohexanoic acid.

2-Methyl-5-oxohexanoic acid (12.4g) was collected at 130-140℃/3~4mmHg (IR: 3180-3020, 2937, 1720, 1462, 1416, 1376, 1166, 1124, 808, 741; MS: 127, 101, 99, 87, 73, 71, 57, 43).

2-Ethyl-5-oxohexanoic acid (10.5g) was collected at 126-134℃/2mmHg (IR: 3160-3018, 2967, 1725, 1462, 1416, 1360, 1227, 1167, 1100, 945, 780; MS: 158(MW), 141, 140, 115, 113, 101, 87, 71, 70, 57, 56, 45, 43, 42).

2-Isopropyl-5-oxohexanoic acid (15.3g) was collected at 128-136℃/2mmHg (IR: 3100-3010, 2965, 2937, 1723, 1468, 1417, 1390, 1370, 1230, 1165, 935, 848; MS: 172(MW), 155, 154, 127, 111, 101, 97, 83, 71, 58, 56, 43).

METHYL AND ETHYL ESTERS OF 2-ALKYL-5-OXOHEXANOIC ACID The acid and methanol or ethanol were refluxed with concentrated sulphuric acid for 6 hrs. The mixture was dried and neutralized with anhydrous potassium carbonate. After removal of the alcohol the ester was obtained by vacuum distillation.

Methyl 2-methyl-5-oxohexanoate was collected at 75-78℃/3mmHg (IR:

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2980,2957,2882, 1737,1720,1464,1437,1365,1265,1206,1164,1128,1018,985,842; MS:158(MW),127,126,115,101,99,71,59,43).

Ethyl 2-methyl-5-oxohexanoate was collected at 82-84℃/4mmHg (IR:2961,2920, 1723,1712,1463,1446,1370,1250,1161,1022,858; MS:172(MW),127,126,115,101, 99, 73,45, 43).

Methyl 2-ethyl-5-oxohexanoate was collected at 80-81℃/3mmHg (IR: 2945,2860, 1725,1710,1606,1468,1413,1382,1350,1143,1071,984,850,797; MS:172(MW),141,140, 115,113,112,71,59,43).

Eehyl 2-ethyl-5-oxohexanoate was collected at 94-96℃/4mmHg (IR:2957, 2852, 1724,1707,1477, 1440,1384,1348,1149,1020,942,857; MS:186(MW), 143, 141, 140, 129,115,112,73,71,57,43).

Methyl 2-isopropyl-5-oxohexanoate was collected at 96-99℃/3mmHg (IR: 2963, 2886,1730, 1713,1462,1433,1370,1251,1198,1157,1047,852; MS:186(MW),155,154, 143,127,115,111,71,57,43).

Ethyl 2-isopropyl-5-oxohexanoate was collected at 103-105℃/3mmHg (IR:2964, 2938,1728,1467,1372,1177,1156,1027,855; MS:200(MW),157,155,154,143,127,112, 111,71,55,43).

Note: IR spectra were determined with a PE-580B IR spectrometer. MS spectra were carried out on a HP-5988 MS spectrometer.

SENSORY TEST All of the prepared acids and esters were injected to blended type and flue-cured type cigarettes at 0.01% of the tobacco weight. The effect of these compounds on cigarette smoke were evaluated by smoking panel.

RESULTS AND DISCUSSION

1. 2-Isopropyl-5-oxohexanoic acid can be synthesised in one-step with the yield of 45.3%. Since the synthesis was completed without the seperation of condensation product, ethyl ethoxycarbonyl-2-isopropyl-5-oxohexanoate, this method is relatively more covenient and applicable than other methods previously reported.

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The other two acid, 2-methyl-and 2-ethyl-5oxohexanoic acid, having the similar skeleton with 2-isopropyl-5-oxohexanoic acid, can also be synthesised with the same method and the yield is 30~45%. And these two acids and their methyl and ethyl esters have not been reported to exist in tobacco.

2. The odor of synthesised compounds and their effect on cigarette smoke are given below.

TABLE

ODOR AND SMOKE FLAVOR OF THE SYNTHESISED COMPOUNDS

Compound	Odor	Smoke Flavor
2-Isopropyl-5-oxohexanoic acid	Hay-like, Fruity, Sour-sweet	Oriental character, Sweet, Mellowing, Slightly Grassy, Smoothing
2-Ethyl-5-oxohexanoic acid	Cream, Sour-sweet	Hay-like, Bitter
2-Methyl-5-oxohexanoic acid	Melon-like, Sweet, Green	Roasted, Flue-cured chracter, Green
Ethyl 2-isopropyl-5-oxohexanoate	Musty, Winey	Smoothing, Adds body, Sour, Sweet
Methyl 2-isopropyl-5-oxohexanoate	Fruity, Musty	Woody, Hay-like, Green, Smoothing
Ethyl 2-ethyl-5-oxohexanoate	Pearlike、Sweet	Sweet、Roasted
Methyl 2-ethyl-5-oxohexanoate	Musty-cereal	Green、Burnt-woody
Ethyl 2-methyl-5-oxohexanoate	Roasted, Green	Sweet, Smoothing, Flue-cured character, Roasted
Methyl 2-methyl-5-oxohexanoate	Almond、Bean	Flue-cured character, Roasted Smoothing, Hay-like

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2-Isopropyl-5-oxohexanoic acid has hay-like, fruity and sour-sweet odor and can give the slightly grassy smell and Oriental tobacco character in cigarette smoke. As the isopropyl radical in C-2 is substituted by methyl to form 2-methyl-5-oxohexanoic acid, the melon-like, green odour and a fruity, roasted flavour on smoke are obtained.

The esters of 2-methyl and 2-isopropyl-5-oxohexanoic acid have similar behavior in cigarete smoke. They enhance and improve the flavor of smoke and reduce the irritation of blended type cigarette as well as flue-cured type cigarette

The effect of 2-ethyl-5-oxohexanoic acid and its methyl and ethyl esters on smoke is not significant.

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